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(54) Title: PHARMACEUTICAL LIQUID COMPOSITION CONTAINING PYRIDONE DERIVATIVE

(57) Abstract: A pharmaceutical liquid composition containing the Pirfenidone in a very high concentration of more or less 25% by weight can be obtained by dissolving the Pirfenidone in diethylene glycol monoethyl ether. Even when the liquid medicinal compositions are stored for a long period of time, the Pirfenidone will not be recrystallized with a good chemical and physical stability. Furthermore, the liquid compositions are little irritating to the wounds on the mucous membrane of the skin and suitable for the manufacture of pharmaceutical formulations to be administered either via the oral, percutaneous, nasal or vaginal routes or by means of spray, patch, inhalation, injection or intravenous drip.

DESCRIPTION

PHARMACEUTICAL LIQUID COMPOSITION CONTAINING PYRIDONE DERIVATIVE

TECHNICAL FIELD

The present invention relates to a pharmaceutical liquid composition containing a pyridone derivative. More particularly, it relates to a pharmaceutical liquid composition containing as the active ingredient a pyridone derivative such as 5-methyl-1-phenyl-2-(1H)-pyridone (Pirfenidone) and the like, which is effective in the treatment of dermatological disorders, particularly fibrotic dermatoses such as fibrotic lesional tissues, contiguous warts and the like or contact dermatitis, keloids, scars after burn surgery and the like. Said liquid compositions containing the pyridone derivative in the high concentrations, with the absence of recrystallization is stable for a long period of time and suitable to be administered orally, percutaneously, nasally or vaginally or as a spray, patch, inhalant, injection or intravenous drip.

BACKGROUND OF THE INVENTION

As described in US Patent No. 5,310,562 and European Laid-Open Patent No. 0383591, the 5-methyl-1-phenyl-2-(1H)-pyridone (Pirfenidone) has found a broad

spectrum of applications in the prevention and treatment of fibrotic disorders, particularly in the reparation and prevention of fibrotic lesional tissues, contiguous warts, contact dermatitis, keloids, fibrosis of the lung, fibrosis and hypertrophy of the prostate, nephrosclerosis and the like; and useful in the treatment of scars after burn surgery, Alzheimer's disease and the like. These literatures have described that the Pirfenidone is generally administered orally or percutaneously or by injection.

With respect to the Pirphenidone pharmaceutical formulations, International Published Application WO00/16775 has described a gel formulation for topical administration, comprising a gel-forming agent such as carboxypolymethylene, a plasticizer such as polypropylene, an antioxidant such as sodium metabisulfite and a pH adjusting agent such as sodium hydroxide. The gel formulation has been described as excellent in stability without the recrystallization of the active ingredient even after it is stored at various temperatures for a long period of time. However, the highest possible concentration of active ingredient is 7% by weight in these gel formulations and it cannot be said that the formulations are capable of containing the active ingredient in a sufficiently high concentration.

Attempts to make the highly concentrated formulations by using alcohol-based solvents as the

solution-forming agent would be frustrated because the solvents irritate the mucous membrane, give rise to pains in open wounds and are not acceptable clinically. In Europe and USA, dimethylsulfoxide (DMSO) has been incorporated into the pharmaceutical formulations for external use as the additive unaccompanied by irritation to the mucous membrane and capable of increasing the solubility of Pirfenidone. However, the DMSO has been found to be problematical from the viewpoint of safety.

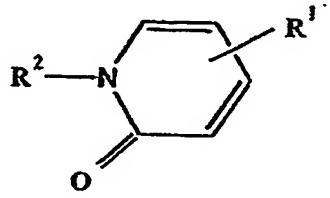
DISCLOSURES OF THE INVENTION

Thus, it has been desired to develop a liquid pharmaceutical formulation capable of containing Pirfenidone as the active ingredient in a high concentration, with the absence of recrystallization during the longtime storage, stable chemically and physically and suitable to be administered either orally, percutaneously, nasally or vaginally or as a spray, patch, inhalant, injection or intravenous drip without causing any problems from the viewpoint of safety.

An intensive investigation was conducted with a view to finding a means for solving the above-mentioned problems. As a result, it has been found that a pharmaceutical liquid composition comprising Pirfenidone in a high concentration of more or less 25% by weight can be obtained by dissolving the active

ingredient in a diethylene glycol monoethyl ether that is a medical solvent called Transcutol-P and described and its safety confirmed in the European and US pharmacopeias. It has also been found that the so obtained composition does not recrystallize if stored for a long period of time, able to be administered either orally, percutaneously, nasally or vaginally or as a spray, patch, inhalant, injection or intravenous drip and certain to make a pharmaceutical composition excellent in every point. The present invention has been brought to completion on the basis of these findings.

The present invention provides a pharmaceutical liquid composition comprising as an active ingredient a pyridone derivative represented by the following formula (I):



(I)

wherein R^1 is an alkyl group optionally having a substituent and R^2 is a phenyl group optionally having a substituent or a pharmaceutically acceptable salt thereof, and a solvent capable of dissolving said active ingredient in a high concentration.

BEST MODE FOR CARRYING OUT THE INVENTION

The pharmaceutical liquid composition of the present invention comprises as the active ingredient a pyridone derivative represented by the above-mentioned formula (I) or a pharmaceutically acceptable salt thereof. In the above-mentioned formula (I), R^1 is an alkyl group optionally having a substituent and R^2 is a phenyl group optionally having a substituent. The examples of the alkyl group optionally having a substituent as R^1 include a C_{1-6} lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl and an alkyl group having a substituent in which said lower alkyl group is substituted with a halogen atom such as fluorine or chlorine; a carboxyl group; an alkoxycarbonyl group such as methoxycarbonyl or ethoxycarbonyl; or a substituent such as amino group. The alkyl group optionally having a substituent as R^1 may be substituted at any of the 3-position, 4-position or 5-position. The examples of the phenyl group optionally having a substituent as R^2 include a phenyl group and a phenyl group having a substituent in which the phenyl group is substituted with a C_{1-6} lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl; a halogen atom such as fluorine or chlorine; a carboxyl group; an alkoxycarbonyl group such as methoxycarbonyl or ethoxycarbonyl; or a substituent such as amino group.

For the pyridone derivative as the active

ingredient, it is preferable to use the 5-methyl-1-phenyl-2-(1H)-pyridone (Pirfenidone) wherein R^1 is a methyl group substituted at the 5-postion and R^2 is a phenyl group.

The pyridone derivative as the active ingredient may be a pharmaceutically acceptable salt thereof. The examples of the salt include an acid addition salt, a salt with alkali or the like. The example of the acid addition salt include an acid addition salt with an acid such as hydrochloric acid, sulfuric acid, phosphoric acid, paratoluene sulfonic acid or methane sulfonic acid. The example of the salt with alkali includes a salt such as sodium salt or potassium salt.

In the liquid composition of the present invention, it is preferable to use the diethylene glycol monoethyl ether (also known as ethoxy diglycol or diethylene glycol ethyl ether) as the solvent capable of dissolving the active ingredient in a high concentration. The diethylene glycol monoethyl ether is a compound represented by the following chemical formula:

$$C_2H_5-O-CH_2-CH_2-O-CH_2-CH_2-OH$$

According to the 3rd and 4th editions of European Pharmacopoeia, the compound occurs as colorless and transparent, well miscible with water,

and has been marketed by the name of Transcutol P as a commonly used solvent. It has also been known that the compound can be used as an absorption promoter in medicine (Ritschel, W. et al., Skin Pharmacol., (1191) 4, 235-245). In the present invention, it is preferable to use the diethylene glycol monoethyl ether having a purity of 99% or higher, more preferably 99.7% or higher and most preferably 99.9% or higher.

The present invention has demonstrated that the Pirfenidone can be dissolved in a very high concentration of more or less 25% by weight by selecting the diethylene glycol monoethyl ether among others as the solvent for Pirfenidone and thus that a liquid medicinal composition containing the Pirfenidone in a very high concentration can be obtained. This high concentration corresponds to the 300 mg dose of the drug in a solution of 2 ml, almost equivalent to the dosage of the same drug in common tablets presently used for oral administration.

In addition to the pyridone derivative, for example, Pirfenidone as the active ingredient and the diethylene glycol monoethyl ether as the solvent, the liquid medicinal composition of the present invention can contain a concentrating agent, antioxidant, dispersant, viscosity adjusting agent, diluent, antimicrobial and the like that are commonly used in medicinal formulations, depending upon the method of administration, the route of administration, the

specific type of formulation and the like. The examples of the concentrating agent include polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and the like. The examples of the antioxidant include sodium metabisulfite, α-tocopherol, sodium ascorbate and the like. The examples of the dispersant include polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose and the like. The examples of the viscosity adjusting agent include bentonite, calcium magnesium silicate and the like. The examples of the diluent include methanol, ethanol and the like. The examples of the antimicrobial include benzalkonium chloride, benzethonium chloride, methylparaben, ethylparaben and the like.

The liquid composition of the present invention has a broad spectrum of application in the administration via oral, percutaneous, nasal or vaginal routes or by means of spray, patch, inhalation, injection or intravenous drip and the like. For example, the highly concentrated solution dissolving the pyridone derivative such as Pirfenidone in the solvent comprising diethylene glycol monoethyl ether is partially separated and the so separated liquid is diluted with water or fruit juice to make a pharmaceutical formulation for oral administration. The liquid composition of the present invention dissolves in a high concentration Pirfenidone which is

slightly soluble in water by nature, accompanied by the hydration property permitting the composition to be diluted 4 to 5 times with water and make a pharmaceutical formulation for oral administration with ease. Furthermore, the liquid composition of the present invention is very low in viscosity and can be filled into a pump spray as a spray formulation or into a roll-on container for use in oral, nasal or vaginal administration. Moreover, it also can be filled into, for example, a vaporizer such as nebulizer, to make a pharmaceutical formulation for vaporizing administration. Furthermore, an injection or intravenous drip can be prepared from the composition by adding isotonic physiological saline thereto.

With respect to the liquid composition of the present invention, the preferred specific examples will be shown below:

Ingredients	% by weight
Pirfenidone	1-25
Diethylene glycol monoethyl ether	70-80
Ethanol (95%)	0-10
Polyvinyl pyrrolidone or hydroxypropyl cellulose	0-3
Sodium metabisulfite	0.02-2
Methyl or propyl paraben	0-0.5
Purified water	0-25

Ingredients	% by weight
Pirfenidone	10-25
Diehtylene glycol monoethyl ether	75-80
Purified water	0-10

Ingredients	% by weight
Pirfenidone	10-25
Diethylene glycol monoethyl ether	75-80
α-Tocopherol	0.1-0.5
Hydroxypropyle cellulose	0-3
Purified water	0-10

The present invention will be explained in detail below, with reference to examples, but the present invention will not be limited by these examples in any way.

Examples 1 to 6:

The pharmaceutical liquid compositions were prepared from the formulations listed in Table 1.

That is, the diethylene glycol monoethyl ether was charged to a suitable container and warmed to 60°C. The Pirfenidone was added while stirring and a yellowish solution was obtained by continuing the stirring until the mixture was transparent. All the

remaining ingredients as listed in Table 1 were dissolved in water at 60°C and this solution was poured into the above Pirfenidone solution and the stirring was continued until mixed uniformly. The so obtained solution was protected from the light. The solutions of Examples 1 and 2 were found to have the viscosity similar to that of water. It was found that the solution of Example 5 had the slightly higher viscosity but was not in a state of gel and still pourable, while the solutions of Examples 3 and 4 were found to have the viscosity similar to that of water.

Table 1

Ingredients	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
Pirfenidone	25.0 g	10.0 g	25.0 g	10.00 g	5.00 g	5.00 g
Diethylene glycol monoethyl ether	75.0 g	80.0 g	70.0 g	80.00 g	80.00 g	80.00 g
Ethanol					5.00 g	5.00 g
Polyvinyl Pyrrolidone					2.96 g	
Hydroxy propyl cellulose						2.96 g
Sodium metabisulfite				0.02 g	0.02 g	0.02 g
Methylparaben or propyl-Paraben				0.02 g	0.02 g	0.02 g
Purified water		10.0 g	5.0 g	9.96 g	7.00 g	7.00 g
Total weight	100.0 g	100.0 g	100.00 g	100.00 g	100.00 g	100.00 g

As shown in Table 1, the liquid compositions containing the Pirfenidone in the high concentrations

could be obtained by dissolving the Pirfenidone in the diethylene glycol monoethyl ether.

Examples 7 to 11:

The liquid compositions were prepared, having the formulations listed in Table 2.

That is, the diethylene glycol monoethyl ether was charged to a suitable container and warmed to 60°C, and the Pirfenidone was added while stirring and a yellowish solution was obtained by continuing the stirring until the whole became transparent. Furthermore, the α-tocopherol was added and water was added while stirring until mixed uniformly. Then, the hydroxypropyl cellulose was added because of its necessity and stirred until a homogenous dispersion was formed. Furthermore, the dispersion was allowed to stand overnight until the particles of hydroxypropyl cellulose, the concentrating agent, were expanded, and finally the product was homogenized. The so obtained dispersion was allowed to stand overnight and a solution in the desired concentration was obtained. The solution was homogenized again and protected from light. The solutions of Examples 7 and 8 were found to have the viscosity similar to that of water.

Table 2

Ingredients	Example 7	Example 8	Example 9	Example 10	Example 11
Pirfenidone	25.0 g	10.0 g	25.0 g	25.0 g	10.0 g
Diethylene glycol monoethyl ether	74.0 g	78.0 g	73.8 g	74.8 g	80.0 g
α-Tocopherol	1.0 g	2.0 g	0.2 g	0.2 g	0.2 g
Hydroxypropyl cellulose			1.0 g		
Purified water		10.0 g			
Total weight	100.0 g	100.0 g	100.0 g	100.0 g	100.0 g

As shown in Table 2, the liquid compositions containing the Pirfenidone in the high concentrations could be obtained by dissolving the Pirfenidone in diethylene glycol monoethyl ether.

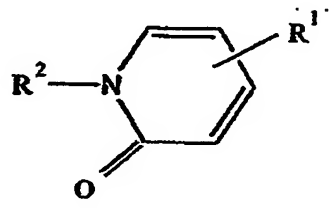
INDUSTRIAL APPLICABILITY

As described above, the Pirfenidone is dissolved in diethylene glycol monoethyl ether, with the result that the liquid medicinal compositions containing the Pirfenidone in very high concentrations of more or less 25% by weight are obtained. When these liquid compositions are stored at low temperatures for a long period of time, the Pirfenidone will not be recrystallized with a good chemical and physical stability. The liquid compositions have a broad spectrum of application in manufacturing the various different pharmaceutical formulations for use in

administration via oral, percutaneous, nasal or vaginal routes or by means of spray, patch, inhalation, Injection or intravenous drip. The liquid compositions can undergo the sterilization in the manufacturing process for injections or intravenous drips and are well miscible when they are diluted in water and non-irritating when applied to the open wounds. Even if the liquid medicinal compositions are contained in non-aqueous pharmaceutical formulations, they will be very stable, having many different advantages.

CLAIMS

1. A pharmaceutical liquid composition comprising as an active ingredient a pyridone derivative represented by the following formula (I):



(I)

wherein R^1 is an alkyl group optionally having a substituent and R^2 is a phenyl group optionally having a substituent or a pharmaceutically acceptable salt thereof, and a solvent capable of dissolving said active ingredient in a high concentration.

2. A pharmaceutical liquid composition according to Claim 1, comprising as the active ingredient a 5-methyl-1-phenyl-2-(1H)-pyridone (Pirfenidone) wherein R^1 is a methyl group at the 5-position and R^2 is a phenyl group in the formula (I) or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical liquid composition according to Claim 1 or 2, wherein the solvent is a diethylene glycol monoethyl ether.

4. A pharmaceutical liquid composition according to Claim 3, wherein the diethylene glycol monoethyl ether has a purity of 99% or higher.

5. A pharmaceutical liquid composition according to any one of Claims 1 to 4, further comprising a

concentrating agent.

6. A pharmaceutical liquid composition according to any one of Claims 1 to 5, further containing an antioxidant.

7. A pharmaceutical liquid composition according to Claim 6, wherein the antioxidant is an α-tocopherol.

8. A pharmaceutical liquid composition according to any one of Claims 1 to 7, which is suitable to be administered orally, percutaneously, nasally or vaginally or as a spray, patch, inhalant, injection or intravenous drip.

9. A pharmaceutical liquid composition according to any one of Claims 1 to 8, having the following components:

Ingredients	% by weight
Pirfenidone	1-25
Diethylene glycol monoethyl ether	70-80
Ethanol (95%)	0-10
Polyvinyl pyrrolidone or hydroxypropyl cellulose	0-3
Sodium metabisulfite	0.02-2
Methyl or propyl paraben	0-0.5
Purified water	0-25

10. A pharmaceutical liquid composition according

to any one of Claims 1 to 8, having the following components:

Ingredients	% by weight
Pirfenidone	10-25
Diethylene glycol monoethyl ether	75-80
Purified water	0-10

11. A pharmaceutical liquid composition according to any one of Claims 1 to 8, having the following components:

Ingredients	% by weight
Pirfenidone	10-25
Diethylene glycol monoethyl ether	75-80
α-Tocopherol	0.1-0.5
Hydroxypropyl cellulose	0-3
Purified water	0-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/16599

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl⁷ A61K 31/4412, 9/08, 9/12, 9/70, 9/72, 47/04, 47/10, 47/14, 47/22, 47/38, A61P 13/08, 13/12, 17/00, 17/02, 17/12, 25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl⁷ A61K 31/4412, 9/08, 9/12, 9/70, 9/72, 47/04, 47/10, 47/14, 47/22, 47/38, A61P 13/08, 13/12, 17/00, 17/02, 17/12, 25/28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Japanese Utility Model Gazette 1922-1996, Japanese Publication of Unexamined Utility Model Applications 1971-2003, Japanese Registered Utility Model Gazette 1994-2003, Japanese Gazette Containing the Utility Model 1996-2003

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 1529960 A (AFFILIATED MEDICAL RESEARCH INC.) 1978.10.25, see the whole document & JP 51-128437 A & US 3974281 A & US 4042699 A & US 4052509 A & BE 836383 A & DE 2555411 A & DK 7505558 A & ZA 7507570 A & CA 1049411 A	1-11
Y	US 3839346 A (AFFILIATED MEDICAL RESEARCH Inc.) 1974.10.01, see the whole document & JP 49-87677 A & DE 2362958 A & DE 2366349 A & NL 7317316 A & BE 816430 A & ZA 7309472 A & FR 2232316 A & DK 7403220 A & GB 1458048 A & GB 1458049 A	1-11

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17.03.2004	13.4.2004

Name and mailing address of the ISA/JP	Authorized officer	
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/JP03/16599

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/47140 A1 (MARGOLIN, SOLOMON, B) 1999.09.23, see the whole document & JP 2002-506820 A & EP 1069898 A1 & AU 9927972 A	1-11
Y	WO 01/58448 A1 (SHIONOGI & CO., LTD.) 2001.08.16, see the whole document & JP 2001-557558 A & AU 200130605 A	1-11
Y	WO 01/78724 A1 (PHARMACIA CORPORATION) 2001.10.25, see the whole document & JP 2004-500427 A & EP 1274425 A1 & US 2002/107250 A1 & AU 200151650 A	1-11
Y	WO 01/47495 A1 (PFIZER PRODUCTS INC.) 2001.07.05, see the whole document & JP 2003-518485 A & US 2002/0006443 A1 & EP 1239835 A1 & AU 200114091 A & BR200016555 A & NO 200202998 A & KR 2002068061 A & CN 1402629 A & ZA200204962 A	1-11
Y	WO 00/41692 A1 (THE PROCTER & GAMBLE COMPANY) 2000.07.20, see the whole document & JP 2002-534402 A & EP 1143973 A2 & US 2002/0086878 A1 & AU 200033449 A & NO 200103440 A & KR 2001093256 A & CN 1346270 A	1-11

(With Respect to Subject Matters for Search)

The term "a solvent capable of dissolving said active ingredient in a high concentration" used in Claim 1 renders the definition of the subject matter of said claim unclear (Article 6 PCT) for the following reason.

A clear definition of "a solvent capable of dissolving said active ingredient in a high concentration" is not disclosed in the description where only diethylene glycole monoethyl ether is concretely exemplified as one of "a solvent capable of dissolving said active ingredient in a high concentration." Besides the scope of the solvent defined as "a solvent capable of dissolving said active ingredient in a high concentration" is not conceivable by skilled person even taking into consideration the general technical knowledge at the time of this application.

Therefore, in this international search report, a partial search was conducted on a basis of diethylene glycole monoethyl ether, the solvent specified in the description.